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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/621,897	07/20/2000	Richard W. Scott	CEPH-1066	4645

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EXAMINER

NGUYEN, DAVE TRONG

ART UNIT

PAPER NUMBER

1632

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8

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.

09/621,897

Applicant(s)

SCOTT ET AL.

Examiner

Dave Nguyen

Art Unit

1632

-- Th MAILING DATE of this communication appears on th cov r sheet with th correspondenc address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 24 October 2001.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-76 is/are pending in the application.
- 4a) Of the above claim(s) 1-38 and 65-76 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 39-64 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.
- If approved, corrected drawings are required in reply to this Office action.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).
- a) ☐ The translation of the foreign language provisional application has been received.
- 15) ☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☒ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____
- 4) ☐ Interview Summary (PTO-413) Paper No(s). _____
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☒ Other: *detailed action*

Applicant's election with traverse of Group X claims (claims 39-64) in the response filed October 24, 2001 is acknowledged.

With respect to the group restriction, the traversal (page 2-3 of the response) is:

1/ the citation of same classes and subclasses for each of Groups II-V demonstrates the lack of serious burden (page 2 of the response);

2/Applicants fail to understand how claims 31-34 (Groups VI-IX) can be classified in to three different classes when they are all directed to compounds identified by the same methods steps of claims 11-14, respectively, particularly since the only difference between claims 11-14 is the mammal employed, sine the only difference between claims 1 and 2 is that claim 1 recites "heterozygous" and claim 2 recites "homozygous"; and

3/ Likewise Groups XI-XIV should be combined into a single group and group XV –XVIII should be combined in to a single group; and

4/ In summary of the traversal, the restriction should be reconsidered, at a minimum, claims 27-30 and 35-38 be combined into a single group, claims 31-34 be combined into a single group, claims 65-68 and 73-76 be combined into a single group, and claims 69-72 be combined into a single group.

The traversal is not found persuasive because:

1/ The fact that multiple distinct inventions are directed to same classes and/or subclasses do not establish applicant's assertion that there will be no serious burden on the examiner for examination of the claims as pending, especially when considering the nature of the each of the inventions and its intended breadth of the respective claims. The nature of all of pending claims, particularly in regard to claims directed to products by process and yet do not distinctly point out any structure of the compound being claim, is that all of these claims which were mainly traversed by applicants are directed to a genus of

unidentified product(s) produced by processes employing distinct material(s). More specifically, each of claims 27-30, 35-38, 31-34, 65-68, 73-76, 69-72 are directed to unspecified compound(s) and/or their respective use that are not limited in anyway to any structure or any starting material(s). Thus, each of the claims is directed to an enormous number of compounds that are yet to be identified. The issue is whether or not these compounds as being claimed in each of the respective claims, *e.g.*, 27-30, 35-38, 31-34, 65-68, 73-76, 69-72, are sharing any substantial common structure so as to constitute the unity of the invention, or at minimum, a generic structure that can be depicted in the form of formula or structure. Given each of the claims as written do no reflect any unified core structure and/or any generic structure that can be depicted in the form of formula or structure, the each of the claims itself does not necessarily embrace compounds that are share by a substantial common structure. Thus, the group restriction among these claims remain proper, notwithstanding the fact that the respective base claims, 19-21, are in any way limited to a particular structure of a starting compound that give rise to the compounds being claims in the claims undergoing the traversal. Should applicant amend 27-30, 35-38, 31-34, 65-68, 73-76, 69-72, so as to point out distinctly a substantial common structure shared by all of the compounds being claimed in these claims, the restriction will be withdrawn by the examiner. Given that no unifying criteria can be established for the claimed compounds and methods of use on the basis of applicant's claims, and given an enormous number of unspecified compounds being claimed in all of the claims that were traversed, a search of one compound claimed in claim 31 does not necessarily overlap with that of another compound claimed in claim 32, particularly given the reasons set forth in the preceding statements. Therefore, a serious undue burden has been established by the examiner in the restriction letter, particularly in view of the nature of the claimed invention and the way the claims were written.

Thus, the Group restriction is proper and made final.

With respect to the species election, Applicant's election with traverse of species of P264L, species of APP695, species of rodent, and species of brain tissue is acknowledged.

Because applicant did not distinctly and specifically point out the supposed errors in the species restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 1-38, and 65-76 have been withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected claimed invention.

Elected claims 39-64 are pending for examination.

The drawings filed July 20, 2000 is not acceptable because of the reasons set forth in the PTO-949 attached to this office action. Correction is required, and the correction may no longer be held in abeyance.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 39-64 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for

A gene-targeted rodent heterozygous for human presenilin-1 (PS-1) mutation and Swedish mutation, said rodent comprising, in its genome, a DNA sequence encoding a functionally active PS-1 protein comprising the human P264L mutation and a DNA sequence encoding a human APP polypeptide having the Swedish APP695 mutation, wherein the A.beta.42 protein level is elevated relative to the A.beta.42 protein level in a wild-type rodent.

does not reasonably provide enablement for any other claimed embodiment embracing any other non-human transgenic non-human mammal. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The claimed invention is directed to a gene-targeted mammal (knock-in mouse which is a transgenic mouse) heterozygous or homozygous for FAD PS-1 mutation comprising a human p264L mutation and for the Swedish APP695 mutation, or a method for screening chemical compounds for the ability to decrease *in vivo* level of A-beta42 peptide, obtaining a tissue sample from said mouse, e.g., brain tissue, non-brain tissue, and body fluids, and measuring the relative amount of A-beta42 peptide in the tissue sample. The specification (pages 37-39) coupled with knowledge in the prior art only provide sufficient guidance and/or evidence for one skilled in the art to make and use the claimed invention directed to A gene-targeted rodent heterozygous for human presenilin-1 (PS-1) mutation and Swedish mutation, said rodent comprising, in its genome, a DNA sequence encoding a functionally active PS-1 protein comprising the human P264L mutation and a DNA sequence encoding a human APP polypeptide having the Swedish APP695 mutation, wherein the A.beta.42 protein level is elevated relative to the A.beta.42 protein level in a wild-type rodent.

Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

The newly amended claims are readable on any gene-targeted non-human mammal heterozygous or homozygous for human Familial Alzheimer's disease (AD). The specification contemplated that the claimed gene-targeted non-human mammal for presenilin-1 (PS-1) mutation and Swedish mutation either exhibits the pathology and symptomatology of ADA, or can be used in a screening assay to screen for *in vivo* inhibitors and for discovering and testing the efficacy and suitability of putative chemicals compounds for their ability to inhibit the formation of A β 42 peptides in the brain tissues, other tissues, and body fluids. However, the specification does not provide sufficient guidance and/or evidence to demonstrate any of the contemplated properties, e.g., ADA phenotypes and/or P264L-

and Swedish APP695 knock in mice that exhibits an increase of endogenous A β 42 peptides relative to that of wild-type mice. While the state of the art of transgenics is such that one skilled in the art can deliver and express a gene in a desired animal, it is not reasonably predictable for one skilled in the art to produce any transgenic animal that exhibit a desired phenotype, regardless whether a gene targeted modification technique rather than a traditional introduction of a desired exogenous protein encoded construct into embryonic cells. Applicants contemplates that by targeting any DNA vector construct encoding any 264 codon-mutant PS-1 gene product (human PS1 mutant cDNA, for example) or a human APP polypeptide comprising the Swedish mutation via homologous recombination into an endogenous genomic site containing the endogenous PS1 gene of any murine cell including murine pluripotent, murine embryo-derived stem (ES) cells, an genetically modified ES cell, for example, can be produced and can be employed to produce a knock-in non-human mammal comprising germ-line chimera as the result of fusion between the genetically modified ES cell and the mouse embryos (page 10). The specification further provides working examples showing the making by ES technology and cross-breeding of a gene-targeted mouse heterozygous for human presenilin-1 (PS-1) mutation and Swedish mutation, said rmouse comprising, in its genome, a DNA sequence encoding a functionally active PS-1 protein comprising the human P264L mutation and a DNA sequence encoding a human APP polypeptide having the Swedish APP695 mutation, wherein the A.beta.42 protein level is elevated relative to the A.beta.42 protein level in a wild-type mouse. However, it is not apparent how such guidance and/or working examples can be reasonably extrapolated to any non-human mammal other than rodent, particularly on the basis of applicant's disclosure and the doubts expressed in the art of record. At the time the invention was made, the art of transgenics including gene targeted modification using ES cell technology was known to be unpredictable with respect to the efficacy of incorporation of transgene, levels of expression as a result of the incorporation, and the phenotypes expressed as a result of the transgene incorporation via homologous recombination in ES cells. Palmiter *et al.* (PNAS, 1991) teach that directed expression of any gene to any specific cell type of an animal by using established transgenic methodology is theoretically possible by combining the regulatory regions(s) of a gene that is expressed in a cell-specific manner with

any mRNA-encoding structural gene. Palmiter *et al.*, note, however, that not all gene constructs work well; the two most common problems are inappropriate expression patterns and failure to achieve adequate expression levels (page 478, left column, first paragraph). Wall (Theriogenology, 1996) discloses the unpredictability of transgene behavior due to factors such as unidentified control elements (during the fusion between ES cell and murine embryos) and may result in variable expression. Whitelaw *et al.* (Transgenic Research, 1991, page 10, column 1 bridging column 2) indicates that exogenous DNA constructs, intronless constructs or constructs containing the introns, do affect variation in gene expression. Palmiter (Ann Rev. Genes, 20, p. 465-498) indicates that variable or inappropriate expressions do often occur in transgenic founder animal and/or offspring (pages 482 and 483).

More specifically as to the lack of reasonable correlation between rodent and other species in ES technology, Polejaeva *et al.* (Theriogenology, Vol. 53, pages 117-126, 2000), states:

Transgenic animals can be successfully produced in a number of species including mice, rabbits, pigs, sheep cattle, and goats by the injection of the gene of interest into the pro-nucleus of a zygote. However, this technique suffers from several serious limitations. The most profound is that DNA can only be added, not deleted, or modified in situ. Also, the integration of foreign DNA is random; this could lead to erratic transgene expression due to the effects at the site of incorporation. In addition, with random integration the possibility exists for the disruption of essential endogenous DNA sequences or activation of cellular oncogenes, both of which would have deleterious effects on the animal's health. Finally, transgenic animals generated using pro-nuclear microinjection are commonly mosaic, i.e., an integrated transgene is not present in all cells. Therefore, the production of the required phenotype coupled to germ line transmission could undue experimentation. See page 119.

In addition, the prior art and post-filing art replete with references, which indicate that ES technology, is generally limited to the mouse system, at present and that only "putative" ES cells exist for other species. See Rulicke *et al.* (Experimental Physiology, Vol. 85, 2000, page 2092), who supports this observation. Rulicke *et al.* disclose, "The ES cell technique, although of great interest in other model organisms and in livestock species, has been successfully used only in mouse so far." Furthermore, the state of the art for chromosomal insertion of DNA into a genetically modified animal as exemplified by Bishop (Heprod. Nutr. Dev, 1998, Vol. 36, pages 607-618) teaches that:

The preferred route to an altered genome is recombination between a transgene and homologous resident DNA in totipotent ES cells followed by introduction of the engineered cells into the inner cell mass of host blastocysts and germline transmission from the resulting chimera. To date, this

approach is available only in mice, because despite a considerable effort, ES cell lines with suitable properties have not been established in other species. See page 608.

As the claims encompass a transgenic mammal comprising modified ES cells by using any technology, and the as-filed specification fails to teach the establishment of true ES cells for use in the production of any transgenic mammal other than rodent, the state of the art supports that only rodent ES cells were enabled for use in the production of transgenic rodent. Taken together, the current status of transgenic art is such that generating transgenic non-human mouse with a requisite phenotype, *e.g.*, FAD, is neither routine nor predictable, unless proven by a working example, let alone a claim that embraces any transgenic non-human mammal other than rodent as claimed. While it is apparent that a skilled artisan can reasonably extrapolate from the exemplified mouse to a rodent having the same DNA constructs embedded in the genome, it is not apparent as to how one skilled in the art reasonably correlates, without undue experimentation, between the mouse and any transgenic non-human mammal other than rodent, *e.g.*, elephant, monkey, dogs, cat, cow, chimpanzee, particularly in view of the foregoing reasons.

Furthermore, the specification provides limited guidance on page 5 with regard to phenotypic expression of the P264L mutation. The specification indicates that the P264L mutation in humans caused an increased amount of amyloid A-beta42 protein, and is involved in clinical manifestation of Alzheimer's disease (AD). However, neither the specification nor its incorporated references provides any teaching on any biological effect on the amount of murine amyloid A-beta42 protein expression or clinical manifestation of AD in the mouse of the invention. Note that incorporation and expression of a human P264L mutant PS1 encoded construct as a foreign genetic construct into any murine cell which is subsequently used for fusion with a murine embryo so as to produce a founder genetically modified mouse does not necessarily mean a reasonable predictability of a phenotypic expression in the founder transgenic mouse for any detectable phenotype and/or phenotypic offspring thereof. Furthermore, there is no evidence either from the specification or from the prior art that an correct introduction via homologous recombination of a human mutant P264L PS-1 gene into a mouse having a murine genome encoding

distinct murine proteins, and having a distinct physiology and chemical pathways would generate any phenotype of FAD.

In other words, while the specification provides sufficient guidance and/or assay systems to screen for *in vivo* inhibitors and for discovering and testing the efficacy and suitability of putative chemical compounds for their ability to inhibit the formation, presence, and deposition of excessive amounts of A-beta42 in any tissues obtained from the claimed transgenic mouse, no specific teachings regarding any other phenotype associated with AD and expressed in any claimed non-human transgenic mammal are disclosed.

The data presented in the as-filed specification support a conclusion of unpredictability and lack of reproducibility. This conclusion coupled with state of the art is consistent with a finding of lack of enablement for the practice of what is claimed. Thus, based upon the evidence in the record, which demonstrates that there is a reasonable basis for questioning the assertions regarding the enablement of the claimed invention, the present claims are properly rejected under 35 U.S.C. 112, first paragraph.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and, *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer.

A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claim 39-64 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-10 of U.S. Patent No. 6,284,924 taken with claims 1-4 of US Pat No. 5,850,003. Although the conflicting claims are not identical, they are not patentably distinct

from each other because both sets of claims embrace a gene-targeted rodent heterozygous for human presenilin-1 (PS-1) mutation and Swedish mutation, said rodent comprising, in its genome, a DNA sequence encoding a functionally active PS-1 protein comprising the human P264L mutation and a DNA sequence encoding a human APP polypeptide having the Swedish APP695 mutation, wherein the A.beta.42 protein level is elevated relative to the A.beta.42 protein level in a wild-type rodent. While the claims of the '924 patent does not explicitly claim a Swedish mutation in the transgenic mice, it would have been obvious for one of ordinary skill in the art to have made or added the Swedish mutation to the mice of the of the '924 patent so as to enhance or induce abnormal neuropathology in the brain of mice. Thus, the claims are obvious variants of one another.

The following prior art is cited to indicate that transgenic mice having a Swedish mutation is routinely made and employed for recombinant assays to identify agents which treats symptoms of Ad disease: US Pat No. 5,877,399.

No claim is allowed.

Any inquiry concerning this communication or earlier communications regarding the formalities should be directed to Patent Analyst Dianiece Jacobs, whose telephone number is **(703) 305-3388**.


Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Deborah Reynolds*, may be reached at **(703) 305-4051**.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is **(703) 305-7401**.

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Nguyen
Primary Examiner
Art Unit: 1632



DAVE T. NGUYEN
PRIMARY EXAMINER